[0396] The lean mice that received treatment are further evaluated at the end of the treatment period for the effects of target inhibition on the expression genes that participate in lipid metabolism, cholesterol biosynthesis, fatty acid oxidation, fatty acid storage, gluconeogenesis and glucose metabolism. These genes include, but are not limited to, HMG-CoA reductase, acetyl-CoA carboxylase 1 and acetyl-CoA carboxylase 2, carnitine palmitoyltransferase I and glycogen phosphorylase, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1, lipoprotein lipase and hormone sensitive lipase. mRNA levels in liver and white and brown adipose tissue are quantitated by real-time PCR as described in other examples herein, employing primer-probe sets that are generated using published sequences of each gene of interest.

What is claimed

1. An oligomeric compound comprising:

a plurality of nucleosides linked together in a sequence;

said sequence comprising at least nucleosides of a first type (F) and nucleosides of a second type (S);

said first and said second types of nucleosides differing in at least one aspect from one another in that they have different 2'-substituent groups; and

when said 2'-substituent groups of said first and said second types of nucleosides are other than H or OH then said oligomeric compound includes at least two nucleosides of said first type and at least one nucleoside of said second type wherein said nucleosides of said first type and said nucleosides of said second type are located with respect to one another such that said sequence includes at least one FSF motif; or

when the 2'-substituent group of one of said first or said second type of nucleoside is H or OH then said oligomeric compound includes at least three nucleosides of said first type and at least three nucleosides of said second type and said nucleosides of said first type and said nucleosides of said second type are located with respect to one another such that said sequence includes at least one FSFSFS motif.

2. The oligomeric compound of claim 1 having at least one portion that is complementary to and capable of hybridizing to a selected nucleic acid target.

3. The oligomeric compound of claim 1 wherein said plurality of nucleosides further includes at least one nucleoside of a third type (T), said third type of nucleoside including a 2'-substituent group and wherein said 2'-substituent group of said third type nucleoside is different from the 2'-substituent group of either of said first and said second type of nucleosides.

4. The oligomeric compound of claim 1 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_2CH_2-O-CH_3, -OC_1-C_{12} alkyl, -O-CH_2-CH_2-CH_2-NH_2, -O-$(CH_2)_2$-O-N$(R_1)_2$, -O-CH_2C(=O)-N$(R_1)_2$, -O-$(CH_2)_2$-O-$(CH_2)_2$-N$(R_1)_2$, -O-CH_2-CH_2-CH_2-NHR_1, -N_3, -O-CH_2-CH=CH_2, -N$HCOR_1$, -NH_2, -NHR_1, -N$(R_1)_2$, -SH, -SR_1, -N(H)OH, -N(H)OR_1, -N(R_1)OH, -N(R_1)OR_1 or -O-CH_2-N(H)-C(=NR_1)[N$(R_1)_2$];

wherein each R_1 is, independently, H, C_1-C_{12} alkyl, a protecting group or substituted or unsubstituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or C_2-C_{12} alkynyl wherein the substituent groups are selected from halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy or aryl; and

wherein said oligomeric compound includes said FSF motif.

5. The oligomeric compound of claim 1 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_3, -O-CH_2CH_2-O-CH_3, -O-CH_2-CH=CH_2, N_3, NH_2, NHOH, -O-$(CH_2)_2$-O-N$(R_1)_2$, -O-CH_2C(O)-N$(R_1)_2$, -O-CH_2-CH_2-CH_2-NH_2, -O-$(CH_2)_2$-O-$(CH_2)_2$-N$(R_1)_2$ or -O-CH_2-N(H)-C(=NR_1)[N$(R_1)_2$];

wherein each R_1 is, independently, H, C_1-C_{12} alkyl, a protecting group or substituted or unsubstituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or C_2-C_{12} alkynyl wherein the substituent groups are selected from halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy or aryl; and

wherein said oligomeric compound includes said FSF motif.

6. The oligomeric compound of claim 1 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_2CH_2-O-CH_3, -O-CH_3, -O-CH_2-CH=CH_2 or -O-CH_2-CH-CH_2-N$H(R_j)$ where R_j is H or C_1-C_{10} alkyl.

7. The oligomeric compound of claim 1 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_3 or -O-CH_2CH_2-O-CH_3.

8. The oligomeric compound of claim 1 wherein said plurality of nucleosides further includes at least one nucleoside of a third type (T), said third type of nucleoside including a 2'-substituent group that is different from the 2'-substituent groups of either of said first or said second type of nucleosides.

9. The oligomeric compound of claim 8 wherein said 2'-substituent group of said third type of nucleoside is H or OH.

10. The oligomeric compound of claim 1 wherein the 2'-substituent group of one of said first or said second type of nucleosides is H or OH and said oligomeric compound includes said FSFSFS motif.

11. The oligomeric compound of claim 1 wherein each of said linked nucleosides is linked by a phosphodiester internucleoside linking group.

12. The oligomeric compound of claim 1 wherein each of said linked nucleosides is linked by a phosphorothioate internucleoside linking group.

13. The oligomeric compound of claim 1 wherein each of said linked nucleosides is, independently, linked by a phophosphodiester or a phosphorothioate internucleoside linking group.

14. The oligomeric compound of claim 1 wherein each of said linked nucleosides is independently linked by an internucleoside linking group wherein said internucleoside linking groups are independently selected from the group consisting of phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 5'-alkylene phosphonate,

chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and boranophosphate.phosphodiester and phosphorothioate.

15. The oligomeric compound of claim 1 comprising at least one motif selected from $F(SF)_n(S)_{nn}$ where n is from 2 to about 20 and nn is 0 or 1.

16. The oligomeric compound of claim 15 comprising at least two motifs independently selected from $F(SF)_n(S)_{nn}$ where n is from 1 to about 20 and nn is 0 or 1.

17. The oligomeric compound of claim 16 comprising two motifs independently selected from $F(SF)_n(S)_{nn}$ where n is from 1 to about 20 and nn is 0 or 1, said two motifs further separated by a region comprising a sequence of nucleosides.

18. The oligomeric compound of claim 17 comprising a sequence of nucleosides joined together such that one of said motifs is located at the 5'-end of said sequence of nucleosides and the other of said motifs is located at the 3'-end of said sequence of nucleosides and said motifs being separated by from about 6 to about 20 nucleosides.

19. The oligomeric compound of claim 1 having the formula X_1-Y-X_2:

wherein

Y is a region of from about 6 to about 18 linked nucleosides; and

each of X_1 and X_2 is, independently, a plurality of linked nucleosides having the formula $F(SF)_n(S)_{nn}$ where n is from 1 to about 20 and nn is 0 or 1.

20. The oligomeric compound of claim 19 wherein each of X_1 and X_2 is, independently, FSFS, FSFSF, FSFSFS, FSFSFSF or FSFSFSFS.

21. The oligomeric compound of claim 20 wherein Y is from about 5 to about 12 linked nucleosides.

22. The oligomeric compound of claim 19 wherein each of said linked nucleosides is linked by a phosphodiester internucleoside linkage.

23. The oligomeric compound of claim 19 wherein each of said linked nucleosides is linked by a phosphorothioate internucleoside linkage.

24. The oligomeric compound of claim 19 wherein each of said linked nucleosides is, independently, linked by a phophosphodiester or a phosphorothioate internucleoside linkage.

25. The oligomeric compound of claim 19 wherein the linked nucleosides selected from $F(SF)_n(S)_{nn}$ are linked by phosphodiester internucleoside linkages, the linked nucleosides comprising the Y region are linked by phosphorothioate internucleoside linkages and each of the $F(SF)_n(S)_{nn}$ motifs are independently linked to the ends of the Y region by a phosphodiester or phosphorothioate internucleoside linkage.

26. The oligomeric compound of claim 19 wherein the linked nucleosides selected from $F(SF)_n(S)_{nn}$ are linked by phosphorothioate internucleoside linkages, the linked nucleosides comprising the Y region are linked by phosphodiester internucleoside linkages and each of the $F(SF)_n(S)_{nn}$ motifs are independently linked to the ends of the Y region by a phosphodiester or phosphorothioate internucleoside linkage.

27. The oligomeric compound of claim 1 having from about 10 to about 40 nucleotides.

28. The oligomeric compound of claim 1 having from about 18 to about 30 nucleotides.

29. The oligomeric compound of claim 1 having from about 21 to about 24 nucleotides.

30. The oligomeric compound of claim 1 further comprising at least one conjugate group.

31. The oligomeric compound of claim 1 further comprising at least one terminal cap moiety.

32. The oligomeric compound of claim 31 wherein said terminal cap moiety is attached to one or both of the 3'-terminal and 5'-terminal ends of said oligomeric compound.

33. The oligomeric compound of claim 32 wherein said terminal cap moiety is an inverted deoxy abasic moiety.

34. A composition comprising a first oligomeric compound and a second oligomeric compound, wherein:

at least a portion of said first oligomeric compound is capable of hybridizing with at least a portion of said second oligomeric compound;

at least a portion of said first oligomeric compound is complementary to and capable of hybridizing to a selected nucleic acid target;

at least one of said first and said second oligomeric compounds comprises at least nucleosides of a first type (F) and nucleosides of a second type (S);

said first and said second types of nucleosides differing in at least one aspect from one another in that they have different 2'-substituent groups; and

when said 2'-substituent groups of said first and said second types of nucleosides are other than H or OH then at least one of said first and said second oligomeric compounds includes at least two nucleosides of said first type and at least one nucleoside of said second type wherein said nucleosides of said first type and said nucleosides of said second type are located with respect to one another such that said first or second oligomeric compound includes at least one FSF motif; or

when the 2'-substituent group of one of said first or said second type of nucleoside is H or OH then at least one of said first and said second oligomeric compounds includes at least three nucleosides of said first type and at least three nucleosides of said second type and said nucleosides of said first type and said nucleosides of said second type are located with respect to one another such that at least one of said first and said second oligomeric compounds includes at least one FSFSFS motif.

35. The composition of claim 34 wherein the 2'-substituent groups of said first and said second types of nucleosides are other than H and OH further comprising at least one of said

first and said second oligomeric compounds having at least two of said nucleosides of said first type (F) and at least two of said nucleosides of said second (S) type wherein said nucleosides of said first and said second types are alternating to give at least one of said first and said second oligomeric compounds having at least one FSFS motif.

36. The composition of claim 34 wherein the 2'-substituent groups of said first and said second types of nucleosides are other than H and OH further comprising at least one of said first and said second oligomeric compounds having at least two of said nucleosides of said first type (F) and at least three of said nucleosides of said second (S) type wherein said nucleosides of said first and said second types are alternating to give at least one of said first and said second oligomeric compounds having at least one FSFSF motif.

37. The composition of claim 34 wherein at least one of said first and said second oligomeric compounds comprise only nucleosides of said first type and said second type and wherein said nucleosides of said first and said second types are alternating throughout the entire sequence of said oligomeric compound.

38. The composition of claim 37 wherein both of said first and said second oligomeric compounds comprise only nucleosides of said first type and said second type and wherein said nucleosides of said first and said second types are alternating throughout the entire sequence of both of said oligomeric compounds.

39. The composition of claim 38 wherein said nucleosides of said first and said second types have 2'-substituent groups other than H and OH.

40. The composition of claim 34 further comprising nucleosides of a third type (T) wherein said nucleosides of said third type are different from said nucleosides of said first and said second type.

41. The composition of claim 40 wherein said nucleosides of said third type have 2'-H or 2'-OH substituent groups.

42. The composition of claim 34 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_2CH_2-O-CH_3, -OC_1-C_{12} alkyl, -O-CH_2-CH_2-CH_2-NH_2, -O-$(CH_2)_2$-O-N$(R_1)_2$, -O-CH_2C(=O)-N$(R_1)_2$, -O-$(CH_2)_2$-O-$(CH_2)_2$-N$(R_1)_2$, -O-CH_2-CH_2-CH_2-NHR_1, -N_3, -O-CH_2-CH=CH_2, -$NHCOR_1$, -NH_2, -NHR_1, -N$(R_1)_2$, -SH, -SR_1, -N(H)OH, -N(H)OR_1, -N(R_1)OH, -N(R_1)OR_1 or -O-CH_2-N(H)-C(=NR_1)[N$(R_1)_2$]; and

wherein each R_1 is, independently, H, C_1-C_{12} alkyl, a protecting group or substituted or unsubstituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or C_2-C_{12} alkynyl wherein the substituent groups are selected from halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy or aryl.

43. The composition of claim 34 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_3, -O-CH_2CH_2-O-CH_3, -O-CH_2-CH=CH_2, N_3, NH_2, NHOH, -O-$(CH_2)_2$-O-N$(R_1)_2$, -O-CH_2C(O)-N$(R_1)_2$, -O-CH_2-CH_2-CH_2-NH_2, -O-$(CH_2)_2$-O-$(CH_2)_2$-N$(R_1)_2$ or -O-CH_2-N(H)-C(=NR_1)[N$(R_1)_2$];

wherein each R_1 is, independently, H, C_1-C_{12} alkyl, a protecting group or substituted or unsubstituted C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or C_2-C_{12} alkynyl wherein the substituent groups are selected from halogen, hydroxyl, amino, azido, cyano, haloalkyl, alkenyl, alkoxy, thioalkoxy, haloalkoxy or aryl; and

wherein said oligomeric compound includes said FSF motif.

44. composition of claim 34 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_2CH_2-O-CH_3, -O-CH_3, -O-CH_2-CH=CH_2 or -O-CH_2-CH-CH_2-NH(R_j) where R_j is H or C_1-C_{10} alkyl.

45. composition of claim 34 wherein the 2'-substituent groups of said first type of nucleosides and said second type nucleosides are, independently, -F, -O-CH_3 or -O-CH_2CH_2-O-CH_3.

46. The composition of claim 34 wherein the 2'-substituent groups of said first type of nucleosides and said second type of nucleosides are independently selected as -F or -O-CH_3.

47. The composition of claim 34 wherein each of said nucleosides of said first and said second type have 3'-endo conformational geometry.

44. The composition of claim 34 wherein said first type of nucleosides are 2'-OH nucleosides.

49. The composition of claim 34 wherein said first type of nucleosides are 2'-H nucleosides.

50. The composition of claim 34 wherein said second type of nucleosides are 2'-fluoro nucleosides.

51. The composition of claim 34 wherein said second type of nucleosides are 2'-O-CH_3 nucleosides.

52. The composition of claim 34 wherein said first type of nucleosides are 2'-fluoro nucleosides and said second type of nucleosides are 2'-O-CH_3 nucleosides.

53. The composition of claim 34 wherein said first oligomeric compound further comprises a 5'-phosphate group.

54. The composition of claim 34 wherein said second oligomeric compound further comprises a 5'-phosphate group.

55. The composition of claim 34 wherein each of said first and said second oligomeric compounds independently, comprise a 5'-phosphate group.

56. The composition of claim 34 wherein said first oligomeric compound comprises a 3'-terminal OH group.

57. The composition of claim 34 wherein the nucleosides of each of said first and said second oligomeric compounds are linked by phosphodiester internucleoside linking groups.

58. The composition of claim 34 wherein the nucleosides of each of said first and said second oligomeric compounds are linked by phosphorothioate internucleoside linking groups.

59. The composition of claim 34 wherein the nucleosides of one said first and said second oligomeric compound are linked by phosphorothioate internucleoside linking groups and the nucleosides of the other of said first and said second oligomeric compound are linked by phosphodiester internucleoside linking groups.

60. The composition of claim 34 wherein the nucleosides of said first oligomeric compound are linked by phosphorothioate internucleoside linking groups and the nucleosides of said second oligomeric compound are linked by phosphodiester internucleoside linking groups.

61. The composition of claim 34 wherein each of the nucleosides of said first and said second oligomeric compound are independently linked by phosphorothioate or phosphodiester internucleoside linking groups.

62. The composition of claim 34 wherein each of the nucleosides of said first and said second oligomeric compound are independently linked by an internucleoside linking group selected from the group consisting of phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 5'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and boranophosphate.

63. The composition of claim 34 wherein each of said first and said second oligomeric compounds comprise only said first and said second type nucleosides and wherein said first and said second type nucleosides are alternating in both of said first and said second oligomeric compounds.

64. The composition of claim 63 wherein said first oligomeric compound has first type nucleosides starting at its 5'-terminus and wherein the first type nucleosides of said first and said second oligomeric compounds align with each other when the first and second oligomeric compounds are hybridized.

65. The composition of claim 63 wherein said first type nucleosides comprise 2'-F or 2'-O-CH_3 groups.

66. The composition of claim 63 wherein said first type nucleosides comprises one of 2'-F or 2'-O-CH_3 groups and the second type nucleosides comprise the other of 2'-F or 2'-O-CH_3 groups.

67. The composition of claim 63 wherein said first oligomeric compound has first type nucleosides starting at its 5'-terminus wherein said first type nucleosides of said first oligomeric compound and said second type nucleosides of said second oligomeric compound align with each other when said first and said second oligomeric compounds are hybridized.

68. The composition of claim 66 wherein said first type nucleosides comprise 2'-F or 2'-O-CH_3 groups.

69. The composition of claim 63 wherein said first type nucleosides comprises one of 2'-F or 2'-O-CH_3 groups and the second type nucleosides comprise the other of 2'-F or 2'-O-CH_3 groups.

70. The composition of claim 63 wherein the nucleosides of said first oligomeric compound are linked with phosphorothioate internucleoside linking groups.

71. The composition of claim 69 wherein the nucleosides of said second oligomeric compound are linked with phosphodiester internucleoside linking groups.

72. The composition of claim 34 further comprising at least one conjugate group.

73. The composition of claim 34 wherein at least one of said first and said second oligomeric compounds further comprises at least one conjugate group attached at the 3'-end, the 5'-end or both the 3'-end and the 5'-end.

74. The composition of claim 34 wherein at least one of said first and said second oligomeric compounds further comprises at least one terminal cap moiety attached at the 3'-end, the 5'-end or both the 3'-end and the 5'-end.

75. The composition of claim 74 wherein said terminal cap moiety is an inverted deoxy abasic moiety.

76. The composition of claim 74 wherein one of said first and second oligomeric compounds is a sense strand and wherein said sense strand comprises a terminal cap moiety at one or both of the 3'-terminal and the 5'-terminal ends.

77. The composition of claim 76 wherein said terminal cap moiety is an inverted deoxy abasic moiety.

78. The composition of claim 34 wherein said first and said second oligomeric compounds are a complementary pair of siRNA oligonucleotides.

79. The composition of claim 34 wherein at least one of said first or second oligomeric compounds comprise at least one motif selected from $F(SF)_n(S)_{nn}$ where n is from 2 to about 20 and nn is 0 or 1.

80. The composition of claim 79 wherein at least one of said first or second oligomeric compounds comprises at least two motifs independently selected from $F(SF)_n(S)_{nn}$ where n is from 2 to about 20 and nn is 0 or 1.

81. The composition of claim 80 wherein said two motifs are separated by a region comprising a sequence of nucleosides.

82. The composition of claim 81 wherein one of said two motifs are located at the 5'-end of one of said first or second oligomeric compounds and the second of said two motifs is located at the 3'-end of the same oligomeric compound and wherein from about 6 to about 20 nucleosides are located between said motifs.

83. The composition of claim 82 wherein said first or second oligomeric compound having said motifs has the formula: X_3-Y_2-X_4:

wherein

Y_2 is a region of from about 6 to about 18 linked nucleosides;

each of X_3 and X_4 is, independently, a plurality of linked nucleosides having the formula $F(SF)_n(S)_{nn}$ where n is from 2 to about 20 and nn is 0 or 1; and

nn is from 1 to about 3.

84. The composition of claim 83 wherein each of X_3 and X_4 is, independently, FSFS, FSFSF, FSFSFS, FSFSFSF or FSFSFSFS.

85. The composition of claim 84 wherein Y_2 is from about 5 to about 12 linked nucleosides.

86. The composition of claim 83 wherein each of said linked nucleosides is linked by a phosphodiester internucleoside linkage.

87. The composition of claim 83 wherein each of said linked nucleosides is linked by a phosphorothioate internucleoside linkage.

88. The composition of claim 83 wherein each of said linked nucleosides is, independently, linked by a phosphodiester or a phosphorothioate internucleoside linkage.

89. The composition of claim 83 wherein the linked nucleosides selected from $F(SF)_n(S)_{nn}$ are linked by phosphodiester internucleoside linkages, the linked nucleosides comprising the Y region are linked by phosphorothioate internucleoside linkages and each of

the $F(SF)_n(S)_{nn}$ motifs are independently linked to the ends of the Y region by a phosphodiester or phosphorothioate internucleoside linkage.

90. The composition of claim 83 wherein the linked nucleosides selected from $F(SF)_n(S)_{nn}$ are linked by phosphorothioate internucleoside linkages, the linked nucleosides comprising the Y region are linked by phosphodiester internucleoside linkages and each of the $F(SF)_n(S)_{nn}$ motifs are independently linked to the ends of the Y region by a phosphodiester or phosphorothioate internucleoside linkage.

91. The composition of claim 34 wherein said first and said second oligomeric compounds are an antisense/sense pair of oligonucleotides.

92. The composition of claim 34 wherein each of said first and second oligomeric compounds has from about 10 to about 40 nucleotides.

93. The composition of claim 34 wherein each of said first and second oligomeric compounds has from about 18 to about 30 nucleotides.

94. The composition of claim 34 wherein each of said first and second oligomeric compounds has from about 21 to about 24 nucleotides.

95. The composition of claim 34 wherein said first oligomeric compound is an antisense oligonucleotide.

96. The composition of claim 34 wherein said second oligomeric compound is a sense oligonucleotide.

97. A composition comprising the oligomeric compound of claim 1 having complementary to and capable of hybridizing to a selected target nucleic acid and at least one protein, said protein comprising at least a portion of a RNA-induced silencing complex (RISC).

98. The composition of claim 97 wherein said oligomeric compound is an antisense oligomeric compound.

99. A composition comprising the composition of claim 34 and at least one protein, said protein comprising at least a portion of a RNA-induced silencing complex (RISC).

100. A method of inhibiting gene expression comprising contacting one or more cells, a tissue or an animal with a composition of claim 34.

101. A method of inhibiting gene expression comprising contacting one or more cells, a tissue or an animal with an oligomeric compound of claim 1.